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Comparative Usefulness of Myocardial Velocity Gradient in Detecting Ischemic Myocardium by a Dobutamine Challenge

HIROSHI TSUTSUI, MD, MASAAKI UEMATSU, MD, PHD,* HIROMI SHIMIZU, MD, MASAKAZU YAMAGISHI, MD, PHD, FACC, NORIO TANAKA, BS, HISAO MATSUDA, MD, PHD,* KUNIO MIYATAKE, MD, PHD, FACC

Suita, Osaka, Japan

Objectives. **We tested the hypothesis that ischemic myocardium can be sensitively detected using tissue Doppler-derived myocardial velocity gradient (MVG) by a dobutamine challenge.**

Background. **Although tissue Doppler imaging (TDI) has recently emerged to quantify regional myocardial contraction, increased translational motion during a dobutamine challenge may affect the measurements. MVG is an indicator of regional myocardial contraction independent of the translational motion.**

Methods. **We studied 19 patients with (n = 13) and without (n = 6) confirmed single-vessel coronary artery disease. Left ventricular short-axis tissue Doppler images were obtained along with conventional echocardiograms during a submaximal two-step dobutamine challenge (10 and 30 μg/kg body weight per min). Endocardial velocity as well as MVG were derived from TDI using computer analysis in the anteroseptal and posterior segments and were compared with visual interpretation.**

Results. **MVG demonstrated a significant dose-responsive increase in the nonischemic segments (anteroseptal: 2.6 ± 0.8/s to 6.0 ± 1.0/s [mean ± SD], p < 0.05; posterior: 3.9 ± 0.7/s to 7.6 ± 1.8/s, p < 0.05) but remained unchanged in the ischemic segments (anteroseptal: 2.5 ± 0.8/s to 2.7 ± 0.7/s, p = NS; posterior: 3.4 ± 1.0/s to 4.1 ± 0.9/s, p = NS). Endocardial velocity failed to clearly demonstrate the differing responses between the nonischemic (anteroseptal: −2.3 ± 1.2 to −2.7 ± 1.6 cm/s, p = NS; posterior: 3.8 ± 1.1 to 7.3 ± 2.7 cm/s, p < 0.05) and ischemic segments (anteroseptal: −2.1 ± 0.5 to −2.8 ± 0.8 cm/s, p = NS; posterior: 4.2 ± 0.8 to 6.5 ± 2.6 cm/s, p = NS). Wall motion abnormality was hardly detectable with visual interpretation (wall motion score range 1.00 to 1.33).**

Conclusions. **Abnormal segments could be sensitively detected by using MVG in a submaximal dobutamine challenge, even where conventional methods failed to detect the abnormality.**

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The recent advent of a tissue Doppler imaging (TDI) technique has enabled tissue motion velocity measurements in real time (1–8). However, because TDI detects the velocity against the transducer, the translational motion of the heart affects the velocity measurement (4). The effect of translation may become particularly augmented when a high dose of dobutamine is given.

The myocardial velocity gradient (MVG), derived from two-dimensional TDI, is an indicator of regional left ventricular contraction that has been proved to be independent of the translational motion (9,10). However, the usefulness of MVG in detecting ischemic myocardium during a dobutamine challenge remains to be determined. Thus, this study sought to 1) assess the feasibility of MVG measurements during a dobutamine challenge to detect ischemic myocardium; and 2) compare the usefulness of MVG with that of tissue Doppler-derived endocardial velocity, along with visual interpretation in patients with confirmed coronary artery disease.

Methods

Study subjects. We enrolled 26 consecutive patients referred to the catheterization laboratory for diagnostic coronary arteriography. Exclusion criteria for the enrollment were 1) multiple coronary artery disease, 2) previous myocardial infarction, 3) valvular or myocardial disease, 4) documented coronary artery spasm, 5) nondominant right coronary artery disease, and 6) atrial fibrillation. Six patients were subsequently excluded because of inadequate echocardiographic images, and one was excluded because he refused a dobutamine challenge. Of the 19 patients studied (15 men, 4 women; mean [±SD] age 60 ± 9 years), 13 had angiographically significant (≥75% obstruction) single-vessel coronary artery disease with exertional chest pain (left anterior descending coronary artery in 7, dominant right coronary artery in 3, left circumflex coronary artery in 3). Six had normal coronary arteries with atypical chest pain, diagnosed as chest pain

From the Cardiology Division of Medicine, National Cardiovascular Center, and *Department of Cardiovascular Dynamics, National Cardiovascular Center Research Institute, Suita, Osaka, Japan. This study was supported in part by Grant-in-Aid for Scientific Research 08670841 from the Ministry of Education, Science and Culture of Japan, Tokyo, Japan. This work was presented in part at the 69th Scientific Sessions of the American Heart Association, New Orleans, Louisiana, November 1996.

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Address for correspondence: Dr. Masaaki Uematsu, Department of Cardiovascular Dynamics, National Cardiovascular Center Research Institute, 5-7-1 Fujishirodai, Suita, Osaka 565, Japan. E-mail: muematsu@res.ncvc.go.jp.

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Abbreviations and Acronyms
ECG = electrocardiogram, electrocardiographic
MVG = myocardial velocity gradient
TDI = tissue Doppler imaging

syndrome. Exercise thallium-201 single-photon emission computed tomography was performed in all patients. Regional myocardial ischemia due to the related coronary artery obstruction included either the anteroseptal or the posterior wall of each patient who had significant coronary artery obstruction. All patients were in sinus rhythm, and informed consent was obtained from all. Five patients had diabetes mellitus, eight had hypertension, and three were taking oral beta-adrenergic blocking agents.

Dobutamine challenge. A two-step submaximal dobutamine challenge was performed within 2 weeks of coronary arteriography. Dobutamine was given intravenously through a peripheral arm vein and was started at a dose of 10 μg/kg body weight per min (low dose). After 3 min, tissue Doppler and conventional echocardiographic images were recorded. On completion of the recording, the dose was increased to 30 μg/kg per min (high dose). Three minutes after the increase of the dose, the tissue Doppler and conventional echocardiographic images were again recorded. The recording time for each step was ~5 to 8 min.

The infusion of dobutamine was stopped before reaching the high dose because of progressive severe angina, ≥2-mm ST segment deviation, clinically significant arrhythmia, systolic blood pressure >200 mm Hg or development of intolerable symptoms, such as severe headache. Blood pressure and the 12-lead electrocardiogram (ECG) were monitored throughout the challenge. Neither dipyridamole nor atropine was added even if the dobutamine challenge was negative at the end of the high dose. Visual interpretation of regional wall motion was done using a four-point scale: 1 = normal; 2 = hypokinesia; 3 = akinesia; 4 = dyskinesia (11). Two expert sonographers who had performed and interpreted >200 dobutamine stress echocardiograms had no knowledge of the other results and interpreted the videotapes of the left ventricular short-axis recordings. Both sonographers agreed with the interpretation.

TDI and MVG. TDI and MVG have been described in detail elsewhere (2,4,9,10). In brief, we used an ultrasound system capable of high frame rate (up to 57 Hz) two-dimensional TDI (SSA-380A, Toshiba Corp.) with a 3.75-MHz sector transducer. MVG was defined as the slope of the regression line of the intramyocardial velocity profile across the myocardial wall (9,12). If the intramyocardial velocity profile can be approximated as linear, MVG is equivalent to the difference in myocardial velocity between the endocardium and epicardium normalized by the wall thickness. Hence, MVG reflects the regional wall thickening (9).

Image acquisition and analysis. We used the parasternal short-axis slice at the level of the papillary muscles. Conventional two-dimensional echocardiograms were recorded on an S-VHS videocassette. Tissue Doppler images were obtained by setting the velocity dynamic range as low as possible to maximize the velocity resolution while avoiding velocity saturation during systole, as had been done in our previous studies (9,10). By reviewing the color display of the cine loop, frames that showed the highest velocity along the endocardium were chosen for the anteroseptal and posterior segments in each systole. A pair of images that comprised a conventional two-dimensional echocardiographic image and a corresponding tissue Doppler velocity image that was set specifically for the computer analysis were simultaneously obtained and transferred to a personal computer (Macintosh 8100, Apple Computer Inc.) through an RGB graphic interface (IG24, Neotec Ltd.) using custom software.

Endocardial velocities in the anteroseptal and posterior segments were also measured with the computer software by depicting the velocities along the endocardium and averaged from 3 consecutive beats.

For MVG measurements, we set the center of the left ventricle in each short-axis echo frame and then traced the endocardium and epicardium. Subsequently, velocity data were automatically corrected by the actual Doppler angle of incidence for each pixel, and the velocity profiles across the left ventricular wall were obtained. MVG was calculated as the slope of each velocity profile by using least squares linear regression. Positive gradients, indicating thickening of the myocardium, were encoded red, and negative gradients, indicating thinning of the myocardium were encoded blue on MVG images (Fig. 1). We measured the segmental MVG from the anteroseptal (~45° around the 12 o'clock position) and from the posterior (~45° around the 6 o'clock position) segments for quantification. Each segmental MVG was averaged from 3 consecutive beats.

Intraobserver and interobserver variability. Reproducibility of MVG measurements during the dobutamine challenge was assessed in 10 randomly allocated segments. The mean difference between the MVG measurements was 0.4 ± 0.2/s. Interobserver variability was also assessed in the same 10 segments by two independent observers (H.T., M.U.). The mean difference between the measurements of the two observers was 0.9 ± 0.5/s. Reproducibility of peak endocardial velocity measurements was also assessed in the same 10 segments. Mean intraobserver difference in the endocardial velocity measurements was 0.3 ± 0.2 cm/s, and the mean interobserver difference was 0.8 ± 0.7 cm/s.

Statistical analysis. Results are expressed as mean value ± SD. Two-way analysis of variance, followed by a Newman-Keuls post hoc test, was performed for repeated measures; $p < 0.05$ was considered statistically significant.

Results

Dobutamine challenge and visual interpretation. Fourteen of the 19 patients completed the two-step protocol. Five patients did not reach the high dose stage because of signifi-

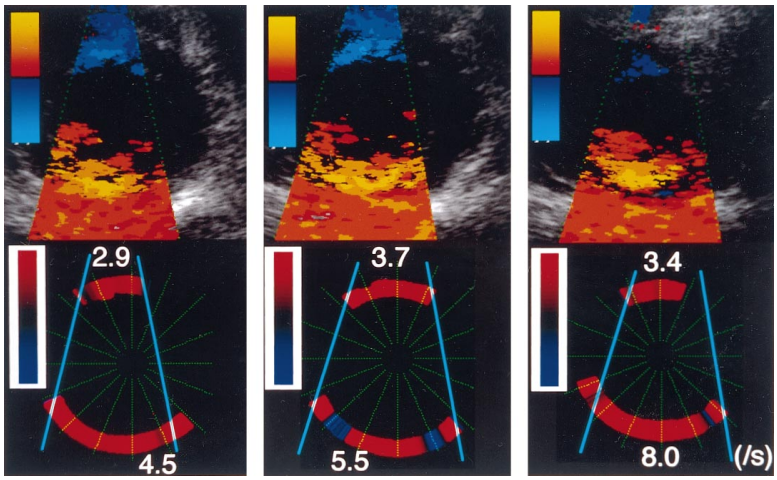


Figure 1. Standard TDI **(top)** and MVG **(bottom)** images of the left ventricular short-axis slice at the level of the papillary muscles during the two-step submaximal dobutamine challenge in a patient with left anterior descending coronary artery obstruction. From **left to right**: before (control) and during low (10 μg/kg per min) and high dose dobutamine (30 μg/kg per min). The anteroseptal wall is color coded **blue** and the posterior wall **red,** depending on the direction of motion in the standard TDI images. In the MVG images, thickening of the myocardium is color coded **red,** and thinning of the myocardium **blue. Numbers** denote segmental MVG (/s) derived from the anteroseptal and the posterior segments. MVG in the posterior segment revealed a dose-responsive increase (from 4.5 to 8.0/s), whereas MVG remained substantially unchanged in the anteroseptal segment (from 2.9 to 3.4/s).

cant ECG changes (n = 2), severe systolic hypertension (n = 1) or intolerable palpitation (n = 2). Of these five patients, three had no significant coronary artery obstruction and one had anterior and one posterior myocardial ischemia. The number of segments analyzed in each subgroup is shown in Table 1. Only one patient developed chest pain, and three had ECG changes indicative of myocardial ischemia. Heart rate increased from 58 ± 8 beats/min at rest to 93 ± 24 beats/min at peak stress. Systolic blood pressure rose from 122 ± 16 mm Hg at rest to 160 ± 29 mm Hg at peak stress.

Among all 104 segments studied, three were interpreted as hypokinesia at rest. Worsening of the wall motion, from normokinesia to hypokinesia, was detected in one patient during the dobutamine challenge. In the other 15 patients, wall motion was interpreted as normal throughout the test. The mean point score ranged from 1.14 to 1.33 in the segments related to significant coronary artery obstruction (ischemic segments) and from 1.00 to 1.08 in the nonischemic segments (Table 1). Overall, segmental abnormalities were barely detectable with visual interpretation. No major complications were encountered during the test.

Endocardial velocity. Peak endocardial velocity was negative in the anteroseptal segments, but was positive in the posterior segments, reflecting the directional difference in wall motion (Fig. 2). Endocardial velocity in the posterior segments showed a tendency toward a dose-responsive increase during the dobutamine challenge, not only in the nonischemic segments, but also in the ischemic segments, although statistical significance was not reached except for nonischemic segments at the high dose (Table 1). In contrast, endocardial velocity in

Table 1. Comparison of Mean Point Scores, Uncorrected Tissue Doppler Endocardial Velocities and Myocardial Velocity Gradients Derived From Nonischemic and Ischemic Segments

	Anteroseptal Segments			Posterior Segments		
		Dobutamine			Dobutamine	
	Baseline	10 μg/kg per min	30 μg/kg per min	Baseline	10 μg/kg per min	30 μg/kg per min
Mean point score						
Nonischemic	1.08 n = 12	1.00 n = 12	1.00 n = 8	1.00 n = 13	1.00 n = 13	1.00 n = 9
Ischemic	1.14 n = 7	1.14 n = 7	1.16 n = 6	1.16 n = 6	1.33 n = 6	1.20 n = 5
Endocardial velocity (cm/s)						
Nonischemic	−2.3 ± 1.2 n = 12	−3.1 ± 1.8 n = 12	−2.7 ± 1.6 n = 7	3.8 ± 1.1 n = 13	5.7 ± 2.5 n = 13	7.3 ± 2.7*† n = 7
Ischemic	−2.1 ± 0.5 n = 7	−3.2 ± 0.9 n = 7	−2.8 ± 0.8 n = 6	4.2 ± 0.8 n = 6	5.7 ± 1.7 n = 6	6.5 ± 2.6 n = 5
MVG (/s)						
Nonischemic	2.6 ± 0.8 n = 10	4.6 ± 1.2* n = 10	6.0 ± 1.0*† n = 5	3.9 ± 0.7 n = 13	6.1 ± 1.5* n = 13	7.6 ± 1.8*† n = 8
Ischemic	2.5 ± 0.8 n = 7	3.1 ± 0.7 n = 7	2.7 ± 0.7‡ n = 6	3.4 ± 1.0 n = 6	3.5 ± 1.0‡ n = 6	4.1 ± 0.9‡ n = 5

*$p < 0.05$ versus baseline. †$p < 0.05$ versus 10 μg/kg per min. ‡$p < 0.05$ versus nonischemic segments. MVG = myocardial velocity gradient. Data presented are mean ± SD or number of segments analyzed.

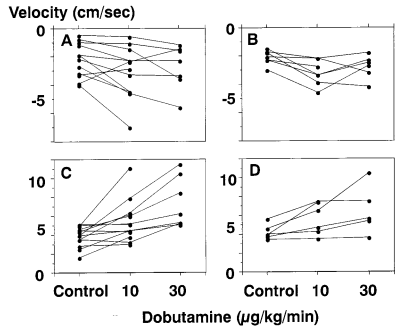


Figure 2. Alterations in the tissue Doppler endocardial velocity (cm/s) derived from each segment during the dobutamine challenge. **A,** Nonischemic anteroseptal segments. **B,** Ischemic anteroseptal segments. **C,** Nonischemic posterior segments. **D,** Ischemic posterior segments.

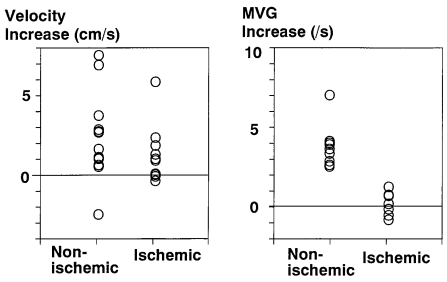
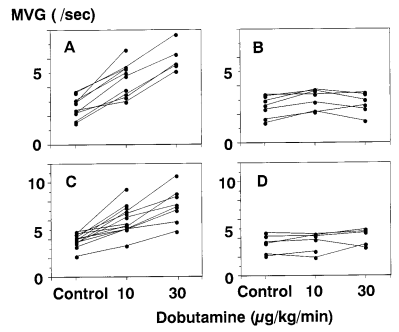


Figure 4. Increases in endocardial velocity **(left)** and in MVG **(right)** at the high dose stage of the dobutamine challenge for ischemic versus nonischemic myocardial segments. Endocardial velocity failed to distinguish between ischemic and nonischemic segments. In contrast, a significant increase in MVG >2.6/s was observed in all nonischemic segments, whereas no ischemic segment showed an increase in MVG >1.5/s.

the anteroseptal segments did not demonstrate a dose-responsive increase during the test, even in the nonischemic segments (Table 1). There was no statistical difference between ischemic and nonischemic segments both in anteroseptal and posterior segments with regard to endocardial velocity (Table 1).

MVG. MVG could be derived from 96 (92%) of 104 segments recorded. MVG in each nonischemic segment demonstrated a dose-responsive increase, whereas MVG in each ischemic segment remained substantially unchanged during the dobutamine stress test (Fig. 3). Statistical significance between the nonischemic and ischemic segments was reached from the low dose stage in the posterior segments (Table 1). Similar results were obtained regarding the anteroseptal segments, although the high dose of dobutamine was required for statistical significance (Table 1). A significant increase in MVG (>2.6/s increase at the high dose stage) was observed in each nonischemic segment, whereas no ischemic segment showed an increase in MVG >1.5/s (Fig. 4). Thus, by using MVG, ischemic segments were distinguished from nonischemic segments, even with a submaximal dobutamine challenge, whereas endocardial velocity failed to characterize ischemic and nonischemic segments.

Figure 3. Alterations in MVG (/s) derived from each segment during the dobutamine challenge. **A,** Nonischemic anteroseptal segments. **B,** Ischemic anteroseptal segments. **C,** Nonischemic posterior segments. **D,** Ischemic posterior segments.



Discussion

TDI has recently been applied to the quantification of dobutamine stress echocardiography (13,14). Although this methodology is promising, several problems remain to be solved. Among them are the effects of translational motion of the heart, which cannot be neglected in certain clinical settings, such as right ventricular volume overload (15–17) or after open heart surgery (18,19). Translational motion is most likely exaggerated when a high dose of dobutamine is given. In the present study, although tissue Doppler endocardial velocity tended to increase in nonischemic segments during the submaximal dobutamine challenge, the difference in endocardial velocity between ischemic and nonischemic segments did not reach statistical significance. This result may be explained by the exaggerated translational motion of the heart. The entire heart shifts upward during systole; therefore, the endocardial velocity in the posterior segment is detected as the sum of the myocardial thickening and the translational velocities, whereas in the anteroseptal segment, the endocardial velocity is detected as the difference between the thickening and translational velocities. Hence, subtle changes in myocardial contraction may well be masked under exaggerated translational motion.

In the present study, worsening of segmental wall motion was only observed in one patient with conventional visual interpretation, which may be explained by the submaximal nature of the dobutamine challenge: 30 μg/kg per min of dobutamine may not have been sufficient to induce significant myocardial ischemia in the majority of our patients with single-vessel coronary artery disease (20,21). It is also noteworthy that single-vessel coronary artery disease has been documented as difficult to diagnose with conventional interpretation, even if the standard dobutamine stress test is performed (22–25). Enhanced adjacent segmental motion or an increase in the translational motion, or both, may affect the interpretation in this disease entity.

Under these circumstances, MVG from the ischemic segments remained substantially unchanged during the dobut-

amine infusion, although wall motion in these segments was apparently observed to be augmented. In contrast, MVG demonstrated a significant dose-responsive increase in all nonischemic segments. Thus, MVG may be more sensitive in detecting subtle wall motion changes than a point score method or tissue Doppler endocardial velocity.

Clinical implications. Although the dobutamine stress test is useful in its present form, its subjective interpretation remains as an unsolved issue. By using MVG, quantitative and objective assessment of wall motion may be possible in dobutamine stress echocardiography. In addition, the dose of dobutamine or atropine, or both, needed to detect ischemic myocardium may be reduced by using MVG to detect the subtle changes in wall motion. In fact, we detected the ischemic segments with a submaximal dobutamine challenge using MVG, where conventional methods failed to demonstrate the abnormality.

Limitations of the study. The small number of myocardial segments and patients assessed in this study should be noted as a limitation. Although assessment of multiple views is indispensable in standard dobutamine stress echocardiography, we could not perform standard dobutamine stress echocardiography with multiple planes because of the prototypic off-line nature of the MVG analysis system available. Nonetheless, MVG has a potential advantage over the conventional methods because MVG could detect ischemic segments even in patients with single-vessel coronary artery disease during submaximal dobutamine challenge, where the conventional methods failed to demonstrate the abnormality. Further advancements in engineering are awaited to facilitate a prospective study that would include a large number and variety of patients with the standard dobutamine protocol, including multiple plane assessment.

Our study cohort included only patients undergoing coronary arteriography, which might bias the "normal" cohort, although we performed thallium scintigraphy to exclude patients with regional abnormalities in myocardial perfusion. In this regard, a large-scale prospective study would be of particular interest once a real-time analysis system was available for clinical use.

Conclusions. The present study demonstrates the comparative usefulness and advantage of MVG over tissue Doppler endocardial velocity, as well as conventional visual interpretation, in detecting ischemic myocardium during a submaximal dobutamine challenge.

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